

FORM PTO-1390 (Modified)
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

293.000218

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

unknown 09/600208

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/DE99/00062

14-January-1999

14-January-1998

TITLE OF INVENTION

OPTICAL ARRANGEMENT IN THE ILLUMINATION BEAM PATH OF A MICROSCOPE

APPLICANT(S) FOR DO/EO/US

Johann ENGELHARDT; Heinrich ULRICH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Acknowledgement postcard

Express Mail Label No. EL628755847US

| | | | | | |
|-------------------------------------------------------------------------------------|--|--------------------------------------------------------|--|-----------------------------------------------|--|
| U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.492(a)(1) - (5)) : 09/600208 | | INTERNATIONAL APPLICATION NO. PCT/DE99/00062 | | ATTORNEY'S DOCKET NUMBER 293.000218 | |
|-------------------------------------------------------------------------------------|--|--------------------------------------------------------|--|-----------------------------------------------|--|

| | | | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|-----------|---------------------------------------------------------|-----------------|
| 21. The following fees are submitted: | | | | CALCULATIONS PTO USE ONLY | |
| BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : | | | | | |
| <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO | | | | \$970.00 | |
| <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO | | | | \$840.00 | |
| <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO | | | | \$690.00 | |
| <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) | | | | \$670.00 | |
| <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) | | | | \$96.00 | |
| ENTER APPROPRIATE BASIC FEE AMOUNT = | | | | \$840.00 | |
| Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30 | | | | \$0.00 | |
| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
| Total claims | 23 - 20 = | 3 | x \$18.00 | | \$54.00 |
| Independent claims | 1 - 3 = | 0 | x \$78.00 | | \$0.00 |
| Multiple Dependent Claims (check if applicable). | | | | <input type="checkbox"/> | \$0.00 |
| TOTAL OF ABOVE CALCULATIONS = | | | | | \$894.00 |
| Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). | | | | <input type="checkbox"/> | \$0.00 |
| SUBTOTAL = | | | | | \$894.00 |
| Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). | | | | <input type="checkbox"/> 20 <input type="checkbox"/> 30 | \$0.00 |
| TOTAL NATIONAL FEE = | | | | | \$894.00 |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). | | | | <input checked="" type="checkbox"/> | \$40.00 |
| TOTAL FEES ENCLOSED = | | | | | \$934.00 |
| | | | | Amount to be: | |
| | | | | refunded | \$ |
| | | | | charged | \$ |

☒ A check in the amount of **\$934.00** to cover the above fees is enclosed.

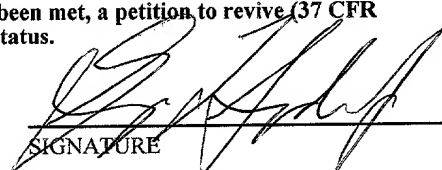
☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
 A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **50-0822** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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 SIGNATURE
 George L. Snyder, Jr.

 NAME
 37,729

 REGISTRATION NUMBER
 July 12, 2000

 DATE

Express Mail Label No. EL 628755847 US

534 Rec'd PCT/PTC 1 2 JUL 2000

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT COOPERATION TREATY**

| | | | |
|-------------|------------------------------------------------------------------|-----------------|------------|
| Applicant: | Johann ENGELHARDT et al. | Group Art Unit: | unknown |
| Serial No.: | unknown | Examiner: | unknown |
| I.A. Filed: | 14-January-1999 | Attorney Ref.: | 293.000218 |
| I.A. No.: | PCT/DE99/00062 | | |
| Title: | OPTICAL ARRANGMENT IN THE ILLUMINATION BEAM PATH OF A MICROSCOPE | | |

PRELIMINARY AMENDMENT

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

Please preliminarily amend the above-identified application, filed concurrently herewith under 35 U.S.C. § 371, as follows:

IN THE SPECIFICATION:

At page 1, line 2 (blank line), please insert:

--CROSS-REFERENCES TO RELATED APPLICATIONS

The present application is the U.S. national phase under 35 U.S.C. 371 of International Application No. PCT/DE99/00062 filed January 14, 1999 claiming priority of German Patent Application No. 198 01 833.9 filed January 14, 1998.

FIELD OF THE INVENTION--;

At page 1, line 5 (blank line), please insert the centered heading --BACKGROUND OF THE INVENTION--;

At page 2, line 10 (blank line), please insert the centered heading --SUMMARY OF THE INVENTION--;

At page 2, lines 16-17, please delete "the features of Claim 1. According to this,";

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At page 2, line 17, please delete "of this kind is";

At page 4, line 29, please delete "which follow Claim 1";

At page 5, line 4, please delete "The drawings show";

At page 5, line 5 (blank line), please insert:

--BRIEF DESCRIPTION OF THE DRAWINGS

The subject matter of the invention is described with reference to the embodiments shown in the drawings.--;

At page 5, line 23 (blank line), please insert the centered heading --DETAILED DESCRIPTION OF THE INVENTION--;

At page 6, after line 27, please insert the following new paragraph:

--The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.--;

At page 8, line 1, please delete "**Patent Claims**" and insert --What is claimed is:--;

IN THE CLAIMS:

Please cancel claim 1-16 and add the following new claims 17-39:

--17. An optical arrangement in an illumination beam path of a confocal laser microscope, said optical arrangement comprising an illumination optical system arranged in said illumination beam path for modifying an illumination diameter of an illumination beam of said microscope.

| Parameter | Value | Standard Error | z-Statistic | p-Value |
|-------------------|--------|----------------|-------------|---------|
| Intercept | 1.0000 | 0.0000 | 1.0000 | 0.0000 |
| Age | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age squared | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age cubed | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age quartic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age quintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age sextic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age septic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age octic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age nonic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age decic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age undecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age duodecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age tredecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age quattuordecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age quindecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age sexdecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age septendecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age octodecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age novemdecic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age unguic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age vicintic | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Age trigintic | | | | |

25. The optical arrangement according to claim 25, wherein said illumination optical system automatically modifies said illumination diameter.

26. The optical arrangement according to claim 18, wherein said illumination optical system is arranged downstream from a point light source of said microscope.

27. The optical arrangement according to claim 18, wherein said illumination optical system is arranged downstream from an optical fiber light source of said microscope.

28. The optical arrangement according to claim 19, wherein said illumination optical system is arranged downstream from a point light source of said microscope.

29. The optical arrangement according to claim 19, wherein said illumination optical system is arranged downstream from an optical fiber light source of said microscope.

30. The optical arrangement according to claim 24, wherein said illumination optical system includes a collimating optical system with a fixed focal intercept and a variable focal length, whereby said illumination diameter is adaptable to the entry pupil of a selected one of said plurality of objectives.

31. The optical arrangement according to claim 18, wherein said illumination optical system includes an expanding optical system for a coupled-in laser beam.

32. The optical arrangement according to claim 19, wherein said illumination optical system includes an expanding optical system for a coupled-in laser beam.

33. The optical arrangement according to claim 32, wherein said illumination beam is variably expandable in accordance with the ratio of the focal length of said variable optical system to the focal length of said expanding optical system.

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39. The optical arrangement according to claim 17, wherein said microscope is a multiphoton laser scanning microscope.--

| Table 1. Demographic characteristics of the study population | |
|--------------------------------------------------------------|-----------------|
| Age (years) | 50.0 ± 10.0 |
| Gender | |
| Male | 50.0% |
| Female | 50.0% |
| Education (years) | 12.0 ± 2.0 |
| Income (USD/month) | 1,000.0 ± 200.0 |
| Marital status | |
| Married | 80.0% |
| Single | 20.0% |
| Occupation | |
| Professional | 30.0% |
| Managerial | 20.0% |
| Technical | 10.0% |
| Service | 20.0% |
| Unemployed | 20.0% |
| Health status | |
| Good | 70.0% |
| Fair | 20.0% |
| Poor | 10.0% |
| Smoking status | |
| Smoker | 30.0% |
| Non-smoker | 70.0% |
| Alcohol consumption | |
| Regular | 10.0% |
| Occasional | 20.0% |
| Never | 70.0% |
| Family size | 3.0 ± 1.0 |
| Number of children | 2.0 ± 1.0 |
| Number of grandchildren | 1.0 ± 1.0 |
| Number of siblings | 2.0 ± 1.0 |
| Number of nephews/nieces | 1.0 ± 1.0 |
| Number of friends | 5.0 ± 2.0 |
| Number of pets | 1.0 ± 1.0 |
| Number of hobbies | 2.0 ± 1.0 |
| Number of religious activities | 1.0 ± 1.0 |
| Number of volunteer activities | 1.0 ± 1.0 |
| Number of community activities | 1.0 ± 1.0 |
| Number of social activities | 1.0 ± 1.0 |
| Number of cultural activities | 1.0 ± 1.0 |
| Number of sports activities | 1.0 ± 1.0 |
| Number of travel activities | 1.0 ± 1.0 |
| Number of shopping activities | 1.0 ± 1.0 |
| Number of dining activities | 1.0 ± 1.0 |
| Number of entertainment activities | 1.0 ± 1.0 |
| Number of learning activities | 1.0 ± 1.0 |
| Number of work activities | 1.0 ± 1.0 |
| Number of household activities | 1.0 ± 1.0 |
| Number of personal care activities | 1.0 ± 1.0 |
| Number of grooming activities | 1.0 ± 1.0 |
| Number of dressing activities | 1.0 ± 1.0 |
| Number of eating activities | 1.0 ± 1.0 |
| Number of drinking activities | 1.0 ± 1.0 |
| Number of sleeping activities | 1.0 ± 1.0 |
| Number of resting activities | 1.0 ± 1.0 |
| Number of thinking activities | 1.0 ± 1.0 |
| Number of feeling activities | 1.0 ± 1.0 |
| Number of acting activities | 1.0 ± 1.0 |
| Number of reacting activities | 1.0 ± 1.0 |
| Number of interacting activities | 1.0 ± 1.0 |
| Number of communicating activities | 1.0 ± 1.0 |
| Number of moving activities | 1.0 ± 1.0 |
| Number of staying activities | 1.0 ± 1.0 |
| Number of going activities | 1.0 ± 1.0 |
| Number of coming activities | 1.0 ± 1.0 |
| Number of leaving activities | 1.0 ± 1.0 |
| Number of arriving activities | 1.0 ± 1.0 |
| Number of departing activities | 1.0 ± 1.0 |
| Number of returning activities | 1.0 ± 1.0 |
| Number of exiting activities | 1.0 ± 1.0 |
| Number of entering activities | 1.0 ± 1.0 |
| Number of passing activities | 1.0 ± 1.0 |
| Number of crossing activities | 1.0 ± 1.0 |
| Number of touching activities | 1.0 ± 1.0 |
| Number of holding activities | 1.0 ± 1.0 |
| Number of carrying activities | 1.0 ± 1.0 |
| Number of lifting activities | 1.0 ± 1.0 |
| Number of lowering activities | 1.0 ± 1.0 |
| Number of pushing activities | 1.0 ± 1.0 |
| Number of pulling activities | 1.0 ± 1.0 |
| Number of twisting activities | 1.0 ± 1.0 |
| Number of bending activities | 1.0 ± 1.0 |
| Number of stretching activities | 1.0 ± 1.0 |
| Number of relaxing activities | 1.0 ± 1.0 |
| Number of resting activities | 1.0 ± 1.0 |
| Number of sleeping activities | 1.0 ± 1.0 |
| Number of waking activities | 1.0 ± 1.0 |
| Number of eating activities | 1.0 ± 1.0 |
| Number of drinking activities | 1.0 ± 1.0 |
| Number of smoking activities | 1.0 ± 1.0 |
| Number of drinking activities | 1.0 ± 1.0 |
| Number of social activities | 1.0 ± 1.0 |
| Number of cultural activities | 1.0 ± 1.0 |
| Number of sports activities | 1.0 ± 1.0 |
| Number of learning activities | 1.0 ± 1.0 |
| Number of work activities | 1.0 ± 1.0 |
| Number of household activities | 1.0 ± 1.0 |
| Number of personal care activities | 1.0 ± 1.0 |
| Number of grooming activities | 1.0 ± 1.0 |
| Number of dressing activities | 1.0 ± 1.0 |
| Number of eating activities | 1.0 ± 1.0 |
| Number of drinking activities | 1.0 ± 1.0 |
| Number of sleeping activities | 1.0 ± 1.0 |
| Number of resting activities | 1.0 ± 1.0 |
| Number of thinking activities | 1.0 ± 1.0 |
| Number of feeling activities | 1.0 ± 1.0 |
| Number of acting activities | 1.0 ± 1.0 |
| Number of reacting activities | 1.0 ± 1.0 |
| Number of interacting activities | 1.0 ± 1.0 |
| Number of communicating activities | 1.0 ± 1.0 |
| Number of moving activities | 1.0 ± 1.0 |
| Number of staying activities | 1.0 ± 1.0 |
| Number of going activities | 1.0 ± 1.0 |
| Number of coming activities | 1.0 ± 1.0 |
| Number of leaving activities | 1.0 ± 1.0 |
| Number of arriving activities | 1.0 ± 1.0 |
| Number of departing activities | 1.0 ± 1.0 |
| Number of returning activities | 1.0 ± 1.0 |
| Number of exiting activities | 1.0 ± 1.0 |
| Number of entering activities | 1.0 ± 1.0 |
| Number of passing activities | 1.0 ± 1.0 |
| Number of crossing activities | 1.0 ± 1.0 |
| Number of touching activities | 1.0 ± 1.0 |
| Number of holding activities | 1.0 ± 1.0 |
| Number of carrying activities | 1.0 ± 1.0 |
| Number of lifting activities | 1.0 ± 1.0 |
| Number of lowering activities | 1.0 ± 1.0 |
| Number of pushing activities | 1.0 ± 1.0 |
| Number of pulling activities | 1.0 ± 1.0 |
| Number of twisting activities | 1.0 ± 1.0 |
| Number of bending activities | 1.0 ± 1.0 |
| Number of stretching activities | 1.0 ± 1.0 |
| Number of relaxing activities | 1.0 ± 1.0 |
| Number of resting activities | 1.0 ± 1.0 |
| Number of sleeping activities | 1.0 ± 1.0 |
| Number of waking activities | 1.0 ± 1.0 |
| Number of eating activities | 1.0 ± 1.0 |
| Number of drinking activities</ | |

Dated: July 12, 2000

534 Rec'd PCT/PTC 1 2 JUL 2000

Optical Arrangement in the Illumination Beam Path of a Microscope

This invention relates to an optical arrangement in the illumination beam path of a microscope, in particular of a confocal laser microscope.

5

In confocal laser microscopy, it has for some time been part of the existing art to expand the laser beam (which of itself is Gaussian) in the illumination beam path, by way of a suitable optical system, in such a way that the entry pupil of the respective objective or objectives usable there is fundamentally overilluminated. The degree of overillumination is an important design parameter. Overillumination of the entry pupil on the one hand provides homogeneous illumination thereof, the purpose being to guarantee the theoretical resolution, in particular in the case of objectives having different apertures. On the other hand, especially in the case of objectives with a small entry pupil, overillumination of the entry pupil results in considerable losses of excitation light. Such losses of excitation light are, however, not acceptable in applications where performance reserves in the excitation light are low.

The Leica TCS laser scanning microscope, for example, in which a fixed expansion optical system is provided, has become known from practical use. The diameter of the laser beam expanded therein is approximately 25 mm ($1/e^2$ value) at the microscope objective.

The divergence of the laser light and thus the illumination of the aperture that is effective for the excitation light can be controlled by modifying the size of the excitation pinhole. Reference is made in this context, solely by way of example, to G.J. Brakenhoff et al. in *Confocal Microscopy Handbook*, J. Pawley, ed., 1994, pp. 87-91.

A PL APO 40X/1.25 objective, for example, has an entry pupil approximately 12 mm in diameter. A PL APO 100X/1.4 objective, on the other hand, has an entry pupil only 5 mm in diameter. As a result, in the latter the excitation light is lost by a factor of $(12/5)^2 = 5.76$ due to unnecessary overillumination.

5

Even if the beam path before the excitation pinhole is otherwise unchanged, the pinhole transmission in proportion to the area of the pinhole is characterized by corresponding light losses at small diameters. This, too, is unacceptable for practical use.

10

It is thus the object of the present invention to describe an optical arrangement in the illumination beam path of a microscope in which optimum illumination is guaranteed while reducing losses of excitation light.

15

The optical arrangement of the generic type according to the present invention achieves the aforementioned object by way of the features of Claim 1. According to this, an optical arrangement of this kind is characterized by an illumination optical system, arranged in the illumination beam path, to modify the illumination diameter.

20

According to the present invention, it has been recognized that the illumination diameter of the illumination beam should be more or less exactly adapted to the entry pupil of the objective in question in order to avoid light losses. Achieving this requires an illumination optical system, arranged in the illumination beam path, with which the illumination diameter can be modified or adapted. In this manner, light losses such as those of the existing art mentioned above can be at least largely avoided.

25

Concretely, the illumination optical system provided according to the present invention could be embodied as an arrangement of replaceable fixed optics. When an

objective is replaced, the fixed optics in the illumination beam path would correspondingly need to be replaced, so that the illumination diameter is matched to the entry pupil of the respective objective.

5 In very particularly preferred fashion, the illumination optical system comprises a variable optical system, preferably operating steplessly, so that it is unnecessary to replace fixed optics in the illumination beam path. The variable optical system can be a preferably motorized zoom optical system, which in turn can be embodied as an ordinary zoom optical system such as is used, for example, in commercially available
10 video cameras.

For simple and optimum adaptation of the illumination diameter to the entry pupils of multiple objectives, an automatic adjustment system could be provided. Concretely, the modification in the illumination diameter could be matched to the entry pupils of
15 predefined objectives, preferably arranged in a revolving nosepiece, the modification or adaptation being accomplished automatically depending on the particular objective being used (corresponding to the position in the nosepiece).

In terms of concrete potential applications of the optical arrangement according to the present invention, it is conceivable for the illumination optical system to be arranged
20 downstream from a point light source or an optical fiber. The illumination optical system could be embodied as a parallelizing optical system with a fixed focal intercept but variable focal length, the beam diameter being adaptable to the entry pupil of the objective.

25 It is also conceivable for the illumination optical system to be embodied as an expanding optical system for a preferably directly coupled-in laser beam. In this context the beam could be variably expandable in accordance with the ratio f_1/f_2 of the focal lengths.

It has already been explained above by way of example that overillumination has been accepted in the existing art, especially when objectives have small entry pupils. The edge illumination in such cases, however, was certainly good. In order to promote edge illumination when an arrangement according to the present invention is used, it is advantageous, in particular with large entry pupils, if the illumination optical system comprises a further optical component that influences or favors edge illumination, the overillumination known from the existing art being avoided in any case. An optical component of this kind could be embodied as an additional lens, as an annular stop, or as a holographically generated optical element, the principal result thereof being that the ordinarily Gaussian laser beam is expanded in the edge regions. For example it would be possible thereby, especially in the case of confocal laser scanning microscopy, to achieve a constant intensity distribution over the entire entry pupil without causing substantial overillumination of the entry pupil of the objective. An intensity profile deviating therefrom may also be advantageous for a specific application.

It is furthermore conceivable to provide, in the case of the arrangement according to the present invention, an additional input for feeding in a further light source, this preferably involving the coupling-in of a laser light beam. With no modification of the actual illumination beam path, this laser light beam could be adaptable to the entry pupil of the objective, thus also making possible in this context an optimization of the laser light beam with no adaptation of the actual illumination beam path.

Lastly, an arrangement of the aforesaid kind could advantageously be used in multiphoton laser scanning microscopy or for multiphoton excitation.

There are various ways of advantageously embodying and developing the teaching of the present invention. Reference is made, for that purpose, on the one hand to the claims which follow Claim 1, and on the other hand to the explanation below of three

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While in FIG. 1 a point light source 2 is depicted (symbolically) as the light source, in FIG. 2 the light is coupled in via an optical fiber 3. In the exemplary embodiment in

FIG. 3, a laser beam 4 or a parallel light beam of an alternative/conventional light source is coupled via a lens 5 directly into illumination beam path 1.

According to the present invention, in all three exemplary embodiments (FIGS. 1, 2, and 3) an illumination optical system 6 is arranged in illumination beam path 1. This illumination optical system 6 serves to modify illumination diameter 7, thus making it possible for illumination diameter 7 to be adapted to the (symbolically depicted) entry pupil 8 of objective 9.

For better comprehension, the Figures show not only illumination beam path 1 as far as object 10, but also a scanner 12 and a beam combiner 11 arranged in illumination beam path 1.

A pinhole optical system 14 and a detection pinhole 15 (depicted schematically) are arranged in detection beam path 13.

In the exemplary embodiments depicted in FIGS. 1 and 2, illumination optical system 6 is embodied as a steplessly operating variable optical system. More precisely, in this case it is a motorized zoom optical system that, however, is shown merely symbolically by way of a shiftable lens 16. Concretely, what is being discussed here is an ordinary zoom optical system such as is known from video cameras.

In the embodiment depicted in FIG. 3, illumination optical system 6 is preceded by a lens 5 into which laser beam 4 is directly coupled.

To avoid repetition, reference is made to the general portion of the Specification regarding further features not evident from the Figures.

Parts List

- | | | |
|----|----|-------------------------------------------|
| | 1 | Illumination beam path |
| | 2 | Point light source |
| 5 | 3 | Optical fiber |
| | 4 | Laser beam |
| | 5 | Lens (downstream from the laser beam) |
| | 6 | Illumination optical system |
| | 7 | Illumination diameter |
| 10 | 8 | Entry pupil of the objective |
| | 9 | Objective |
| | 10 | Object |
| | 11 | Beam combiner |
| | 12 | Scanner |
| 15 | 13 | Detection beam path |
| | 14 | Pinhole optical system |
| | 15 | Detection pinhole |
| | 16 | Lens (of the illumination optical system) |

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Patent Claims

1. An optical arrangement in the illumination beam path of a microscope, in particular of a confocal laser microscope, **characterized by** an illumination optical system, arranged in the illumination beam path, to modify the illumination diameter.
2. The arrangement as defined in Claim 1, **wherein** the illumination optical system is embodied as an arrangement of replaceable fixed optics.
3. The arrangement as defined in Claim 1, **wherein** the illumination optical system comprises a variable optical system, preferably operating steplessly.
4. The arrangement as defined in Claim 3, **wherein** the variable optical system is a preferably motorized zoom optical system.
5. The arrangement as defined in Claim 4, **wherein** the zoom optical system is a zoom optical system usual in video cameras.
6. The arrangement as defined in one of Claims 1 through 5, **wherein** the modification in the illumination diameter is matched to the entry pupils of predefined objectives, preferably arranged in a revolving nosepiece, and preferably is accomplished automatically.
7. The arrangement as defined in one of Claims 2 through 6, **wherein** the illumination optical system is arranged downstream from a point light source or an optical fiber (3).

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14. The arrangement as defined in Claim 11, **wherein** the further optical component is embodied as a holographically generated optical element.

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16. The use of an arrangement as defined in one of Claims 1 through 15 in multiphoton laser scanning microscopy.

Figure 1 consists of 14 subplots (a-n) showing the distribution of various parameters for 1000 simulated patients. The parameters are: (a) Age, (b) Sex, (c) Weight, (d) Height, (e) BMI, (f) Systolic blood pressure, (g) Diastolic blood pressure, (h) Heart rate, (i) Mean arterial pressure, (j) Total cholesterol, (k) LDL cholesterol, (l) HDL cholesterol, (m) Triglycerides, and (n) Fasting glucose. Each subplot shows a bar chart with the frequency of values on the y-axis and the parameter value on the x-axis. The distributions are color-coded: blue for the first 250 patients, green for the next 250, red for the next 250, and yellow for the last 250. The distributions are generally bell-shaped, with some parameters showing more variability than others.

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[illegible]

Fig. 1

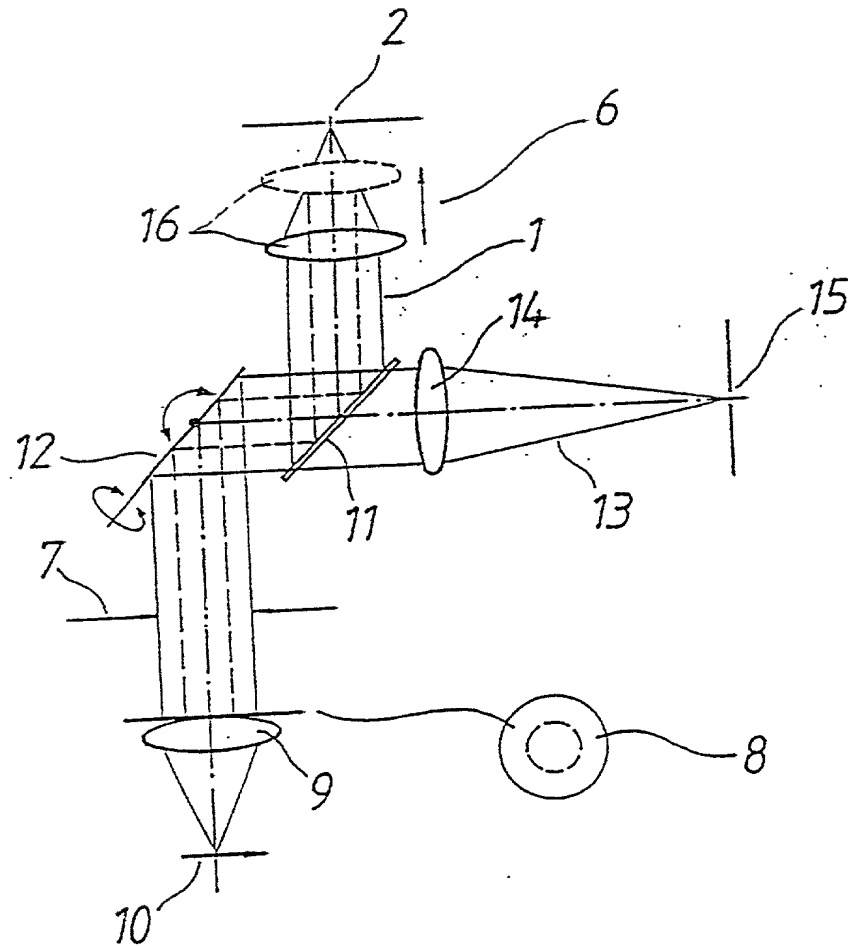


Fig.2

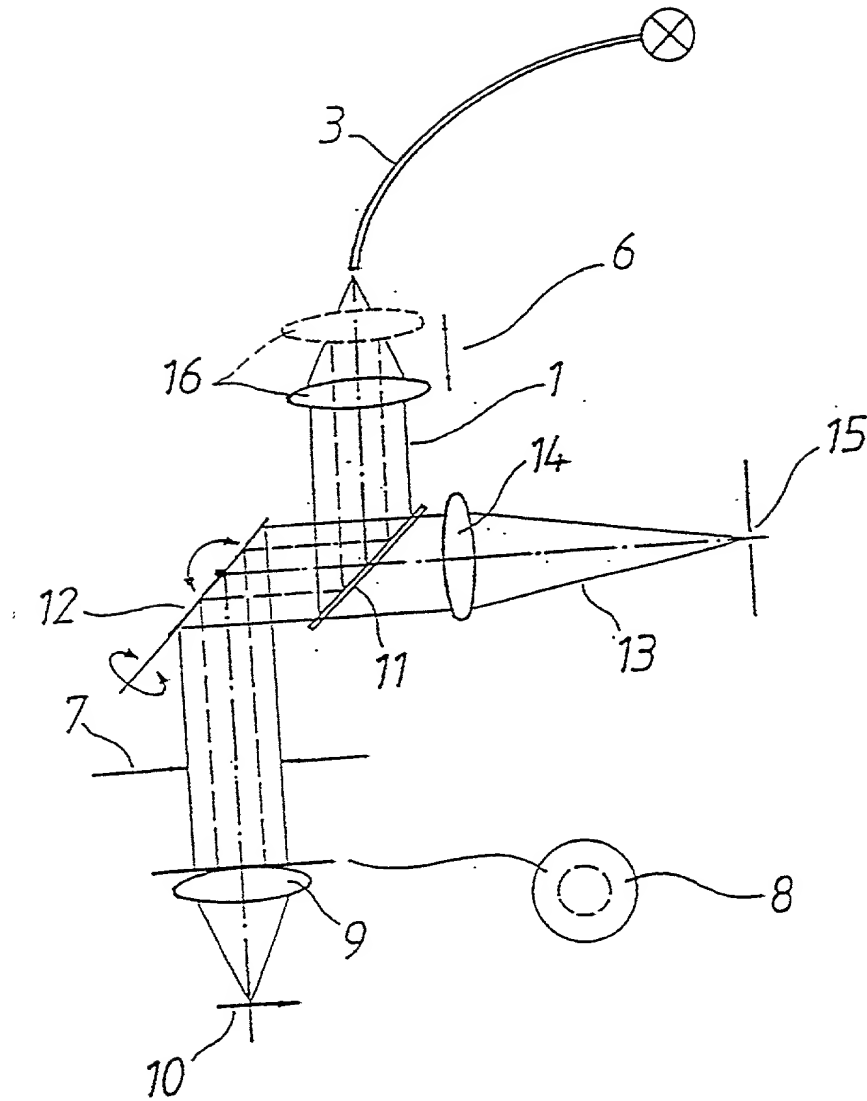
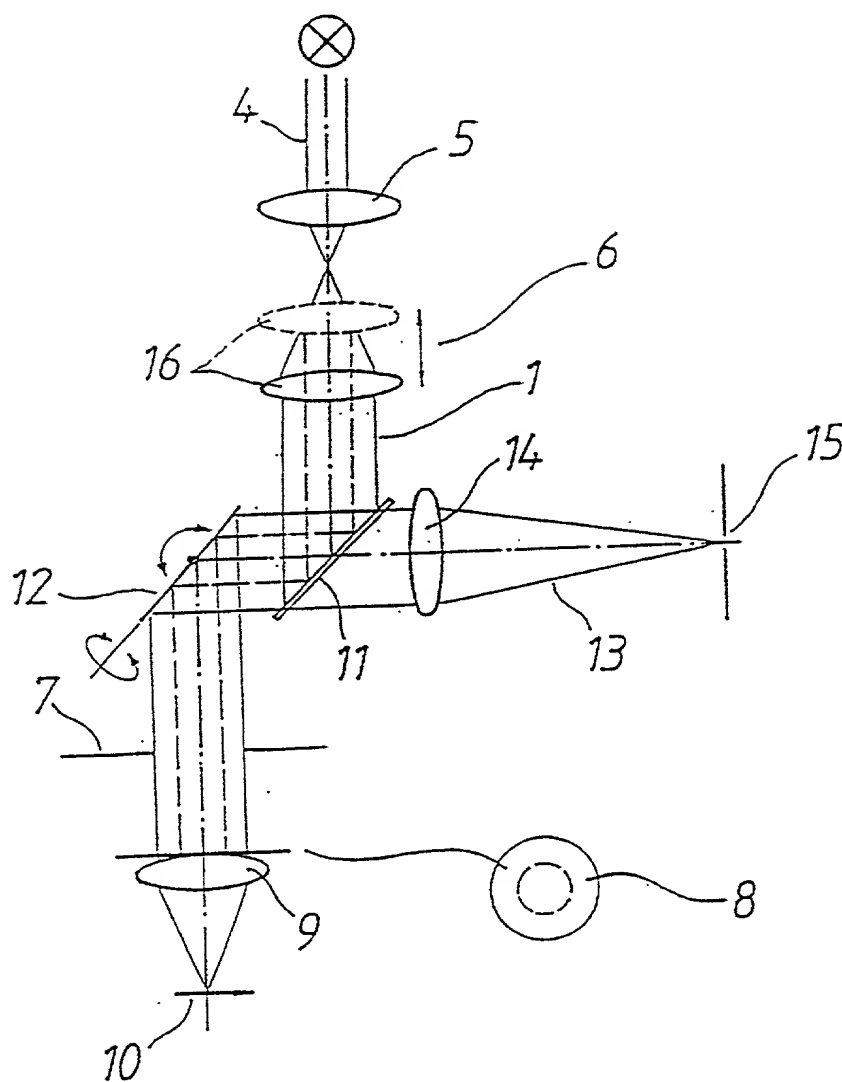


Fig. 3



Declaration and Power of Attorney for Patent Application

Erklärung für Patentanmeldungen mit Vollmacht

German Language Declaration

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**OPTISCHE ANORDNUNG
BELEUCHTUNGSSTRAHLENGANG
MIKROSKOPS** **IM
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daren Beschreibung hier beigefügt ist, es sei denn (in diesem Falle Zutreffendes bitte ankreuzen), diese Erfindung

- ☒ wurde angemeldet am 14 Januar 1998 unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT) PCT/DE99/00062 und am _____ abgeändert (falls zutreffend).

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As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**OPTICAL ARRANGEMENT IN THE ILLUMINATING
BEAM OF A MICROSCOPE**

the specification of which is attached hereto unless the following box is checked:

- ☒ was filed on January 14, 1999 as United States Application Number or PCT International Application Number PCT/DE99/00062 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications
(Frühere ausländische Anmeldungen)

198 01 833.9 Germany 14/January/1998

App. No. Country Day/Month/Year

App. No. Country Day/Month/Year

Ich beanspruche hiermit Prioritätsvorteile unter Title 35, US Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

App. No. Filed:

App. No. Filed:

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App. No. Filed:

App. No. Filed:

Ich erkläre hiermit, daß alle in der vorliegenden Erklärung von mir gemachten Angaben nach bestem Wissen und Gewissen der Wahrheit entsprechen, und ferner daß ich diese eidesstattliche Erklärung in Kenntnis dessen ablege, daß wissentlich und vorsätzlich falsche Angaben oder dergleichen gemäß § 1001, Title 18 des US-Code strafbar sind und mit Geldstrafe und/oder Gefängnis bestraft werden können und daß derartige wissentlich und vorsätzlich falsche Angaben die Rechtswirksamkeit der vorliegenden Patentanmeldung oder eines aufgrund deren erteilten Patentes gefährden können.

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Priority Not Claimed
(Priorität nicht beansprucht)

☐

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I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Status: Patented/Pending/Abandoned

Status: Patented/Pending/Abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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